



16304

PTO/SB/21 (08-03)

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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/897,772
Filing Date	June 29, 2001
First Named Inventor	Keith D. Allen
Art Unit	1636
Examiner Name	Celine X. Qian
Attorney Docket Number	R-268

Total Number of Pages in This Submission

ENCLOSURES (Check all that apply)

- | | | |
|---|--|--|
| <input checked="" type="checkbox"/> Fee Transmittal Form
<input type="checkbox"/> Fee Attached
<input checked="" type="checkbox"/> Amendment/Reply
<input type="checkbox"/> After Final
<input type="checkbox"/> Affidavits/declaration(s)
<input type="checkbox"/> Extension of Time Request
<input type="checkbox"/> Express Abandonment Request
<input type="checkbox"/> Information Disclosure Statement
<input type="checkbox"/> Certified Copy of Priority Document(s)
<input type="checkbox"/> Response to Missing Parts/Incomplete Application
<input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53 | <input type="checkbox"/> Drawing(s)
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<input type="checkbox"/> CD, Number of CD(s) _____ | <input type="checkbox"/> After Allowance communication to Technology Center (TC)
<input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences
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<input type="checkbox"/> Proprietary Information
<input type="checkbox"/> Status Letter
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Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Kelly L. Quast, Reg. No. 52,141 <i>Kelly L. Quast</i>
Signature	
Date	August 22, 2003

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Typed or printed name	Kelly L. Quast		
Signature	<i>Kelly L. Quast</i>	Date	August 22, 2003

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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AUG 25 2003

PTO/SB/17 (08-03)

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**FEE TRANSMITTAL
for FY 2003**

Effective 01/01/2003. Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27**TOTAL AMOUNT OF PAYMENT** (\$ 205.00)**Complete if Known**

Application Number	09/897,772
Filing Date	June 29, 2001
First Named Inventor	Keith D. Allen
Examiner Name	Celine X. Qian
Art Unit	1636
Attorney Docket No.	R-268

METHOD OF PAYMENT (check all that apply)☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None☒ Deposit Account:Deposit
Account
Number
Deposit
Account
Name

50-1271

Deltagen, Inc.

The Director is authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☐ Credit any overpayments☐ Charge any additional fee(s) during the pendency of this application☐ Charge fee(s) indicated below, except for the filing fee
to the above-identified deposit account.**FEE CALCULATION****1. BASIC FILING FEE**

Large Entity Fee Code	Small Entity Fee Code	Fee Description	Fee Paid
1001 750	2001 375	Utility filing fee	
1002 330	2002 165	Design filing fee	
1003 520	2003 260	Plant filing fee	
1004 750	2004 375	Reissue filing fee	
1005 160	2005 80	Provisional filing fee	

SUBTOTAL (1) (\$)**2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE**

Total Claims	Extra Claims	Fee from below	Fee Paid
Independent Claims	-20** =	X	
Multiple Dependent	-3** =	X	

Large Entity Fee Code	Small Entity Fee Code	Fee Description	Fee Paid
1202 18	2202 9	Claims in excess of 20	
1201 84	2201 42	Independent claims in excess of 3	
1203 280	2203 140	Multiple dependent claim, if not paid	
1204 84	2204 42	** Reissue independent claims over original patent	
1205 18	2205 9	** Reissue claims in excess of 20 and over original patent	

SUBTOTAL (2) (\$)

**or number previously paid, if greater. For Reissues, see above

FEE CALCULATION (continued)**3. ADDITIONAL FEES**

Large Entity Fee Code	Small Entity Fee Code	Fee Description	Fee Paid
1051 130	2051 65	Surcharge - late filing fee or oath	
1052 50	2052 25	Surcharge - late provisional filing fee or cover sheet	
1053 130	1053 130	Non-English specification	
1812 2,520	1812 2,520	For filing a request for ex parte reexamination	
1804 920*	1804 920*	Requesting publication of SIR prior to Examiner action	
1805 1,840*	1805 1,840*	Requesting publication of SIR after Examiner action	
1251 110	2251 55	Extension for reply within first month	
1252 410	2252 205	Extension for reply within second month	205.00
1253 930	2253 465	Extension for reply within third month	
1254 1,450	2254 725	Extension for reply within fourth month	
1255 1,970	2255 985	Extension for reply within fifth month	
1401 320	2401 160	Notice of Appeal	
1402 320	2402 160	Filing a brief in support of an appeal	
1403 280	2403 140	Request for oral hearing	
1451 1,510	1451 1,510	Petition to institute a public use proceeding	
1452 110	2452 55	Petition to revive - unavoidable	
1453 1,300	2453 650	Petition to revive - unintentional	
1501 1,300	2501 650	Utility issue fee (or reissue)	
1502 470	2502 235	Design issue fee	
1503 630	2503 315	Plant issue fee	
1460 130	1460 130	Petitions to the Commissioner	
1807 50	1807 50	Processing fee under 37 CFR 1.17(q)	
1806 180	1806 180	Submission of Information Disclosure Stmt	
8021 40	8021 40	Recording each patent assignment per property (times number of properties)	
1809 750	2809 375	Filing a submission after final rejection (37 CFR 1.129(a))	
1810 750	2810 375	For each additional invention to be examined (37 CFR 1.129(b))	
1801 750	2801 375	Request for Continued Examination (RCE)	
1802 900	1802 900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$)**SUBMITTED BY**

(Complete if applicable)

Name (Print/Type)	Kelly L. Quast	Registration No (Attorney/Agent)	52,141	Telephone	650-569-5100
Signature	<i>Kelly L. Quast</i>	Date	August 22, 2003		

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/897,772	06/29/2001	Keith D. Allen	R-268	9809

7590 03/25/2003
DELTAGEN, INC.
1003 Hamilton Avenue
Menlo Park, CA 94025



EXAMINER

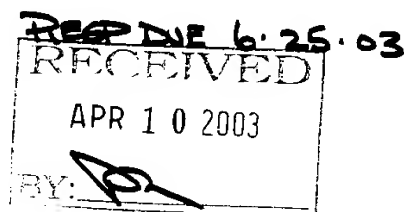
QIAN, CELINE X


ART UNIT PAPER NUMBER

1636

DATE MAILED: 03/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.



	Application No.	Applicant(s)	
	09/897,772	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 January 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-27 is/are pending in the application.
- 4a) Of the above claim(s) 13-16 and 23-27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-12 and 17-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 June 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other:

DETAILED ACTION

Claims 1-27 are pending in the application.

Election/Restrictions

Applicant's election without traverse of Group I in Paper No. 11 is acknowledged.

Groups II and III are rejoined with Group I.

Accordingly, claims 13-16 and 23-27 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1-12 and 17-22 are pending in the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 and 17-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . . [emphasis added]." The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such

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descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

The claims encompass a target construct, a cell or a non-human animal comprising a disruption of "a BMP gene." BMP is a family of genes that are involved in bone differentiation which include BMP2-7. The specification only discloses the disruption of a BMP gene represented by SEQ ID NO:1 in a mouse and targeting constructs made by using the nucleic acid sequence of SEQ ID NO:1. The specification discloses that homozygous disruption of this gene result in mice with kinky tail, low body weight or short body length. The specification fails to disclose targeting constructs of other BMP gene or animals having disruption in other BMP gene. It is unclear whether disruption of other BMP genes in mice or other animals would result in the disclosed phenotype. The structural functional relationship between gene disruption and disclosed phenotype is missing. As such, the specification neither describes the invention by its complete structure nor other identifying characteristics. Therefore, the specification fails to describe the invention in such a way to reasonably convey one skilled in the art that the inventors had possession of the invention at the time the application was filed.

Claims 5-12 and 17-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic knock out mouse having in its genome a homozygous deletion of the BMP gene of SEQ ID NO:1, wherein said mouse exhibits the phenotype of kinky tail, low body weight or short body length; a method of making said mouse and methods of using said mouse to identifying agents that ameliorate the symptoms of said

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mouse, does not reasonably provide enablement for any transgenic and/or knockout animal comprising any disruption in any BMP gene. Further, the specification is not enabling for a knockout mouse comprising any disruption in any BMP gene and for any cell comprising any disruption in a BMP gene and methods of using said mouse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

The nature of the invention is a transgenic non-human animal whose genome comprises a disruption in its endogenous BMP gene, wherein said animal exhibits kinky tail, low body weight and short body length. The claims are further drawn to a method of making said transgenic non-human animal, cells isolated from said animal.

The breadth of claims is very broad. In the instant case, claims 5-10 and 17-19 are drawn to a transgenic non-human animal containing a disrupted endogenous BMP gene wherein such disruption encompass any mutation including insertion, deletion, missense and frameshifts in any place of the gene including promoter, enhancer or a splice site (page 7, second paragraph).

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The claims also encompass such a disruption in any BMP gene. Thus, the claims encompass any transgenic non-human animal containing any type of mutation or disruption in a BMP gene regardless of the phenotype. In addition, claims 10 and 18 encompass the method of generating a BMP knockout mouse using any type of recipient cell. Moreover, the claims also encompass methods of identifying agents that modulates the expression or function of a BMP by using the non-human animal containing a disruption of a BMP gene.

The amount of guidance and working example in the specification is limited. The specification does not provide an enabling disclosure to make said transgenic animal except a BMP (represented by SEQ ID NO:1) knockout mouse. The specification also fails to teach how to use a transgenic animal with said genotype but without a particular phenotype. The phenotype of the knockout animal is the essential element that is required to practice the use of the invention. Further, the specification fails to teach how to identify agents that modulates the expression or function by using a non-human animal that do not express BMP gene. Without teaching from the specification, one skilled in the art would have to turn to prior art for guidance to make and use the transgenic animal as claimed.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan: When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg. 1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol. 20:1425-1429). The specification discloses the phenotype of a homozygous BMP (represented by SEQ ID NO:1) knockout mouse. However, the claims

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encompass heterozygotes, but since heterozygotes have one functional allele, the heterozygotes would not be expected to have the same phenotype as the homozygotes. Thus, the phenotype of a heterozygous transgenic or knockout animal is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic and/or knock out animals that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification. In addition, the transgene expression and the physiological consequences of transgene products are not always accurately predicted in transgenic mouse studies (pg.62, paragraph 1, lines 7-9 in Wall, R.J. 1996. *Theriogenology* 45:57-68). The particular genetic elements required for optimal expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall, 1996). Therefore, in the absence of specific guidance and working examples, the production of transgenic animals with the phenotypes disclosed in the instant application is unpredictable. Thus, the specification is only enabling for a homozygous PDE7A knockout mouse with disclosed phenotype.

The specification fails to provide an enabling disclosure for the generation of other species of transgenic animals besides mice having a disruption in the BMP (represented by SEQ ID NO:1) gene because the guidance offered in the specification is limited to the generation of mice harboring such mutations and no teachings or guidance are offered with regard to how one would generate any other type of animal. Since homologous recombination is required for gene targeting methods such as employed in the instant invention, embryonic stem (ES) cell must be available to carry out the method. To date, there is no teaching from the art that homologous recombination in a somatic cell and subsequent introduction of said cell to a blastocyst would

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generate an offspring carrying said gene mutation. The specification does not teach such a method either. The only species in which the ES is available is the mouse (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmot, 1997 acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p.65). Likewise, Mullins et al. (1996, Clin. Invest. Vol 97, no. 7, 1557-1560) teach that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (p.1558, column 2, paragraph 1). Therefore, no knockout animals can be made for any species other than the mouse at the time of filing. As such, the invention while being enabled for a homozygous knockout mouse, generated by using ES cells, containing homozygous disruption for the BMP (represented by SEQ ID NO:1) gene exhibits phenotype of kinky tail, low body weight and short body length, does not support the enablement of any other BMP knockout animals.

The prior art teaches that there is a family of BMPs that involves in bone differentiation but each has its distinct function (Current opinion in Genetics and Development, 1994, vol.4, pages 737-744). These BMPs are designated as BMP2-7. It is unclear whether the BMP represented by SEQ ID NO:1 belongs in this group or it is a novel BMP. As such, whether disrupting any other BMP in a transgenic knockout animal would result in the disclosed phenotype is unpredictable. In addition, the specification does not support the enablement of any cells comprising the disruption of any BMP or cells derived from the BMP knockout mouse

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because the disclosed phenotype of the BMP knockout mouse cannot be observed in a cell. The cell having disruption of a BMP gene cannot exhibit kinky tail, low body weight or short body length. The specification fails to teach how to use a BMP disrupted cell without any phenotype.

In view of the limited guidance in the specification and the unpredictability of the art, one skilled in the art would have to engage in undue amount of experimentation make and use the invention in commensurate with the scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 9, 10 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 1-4 and 10, the term "selection marker," "selectable marker" or "screening marker" renders the claims indefinite because it is unclear how a protein can be contained in a nucleic acid construct.

Regarding claims 9 and 19, the word "derived" renders the claims indefinite because the number and nature of the derivative process is unknown. As such, the metes and bounds of the claims cannot be established.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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Claims 1-10 rejected under 35 U.S.C. 102(b) as being anticipated by Luo et al (Genes & Development, 1995, Vol 9, pages 2808-2820).

Luo et al. disclose a BMP-7 knockout mouse (see page 2810, 1st col., 2nd paragraph). Luo et al. also disclose a method of making said mouse use embryonic stem cell technology (see abstract and page 2809, 2nd col., 2nd paragraph). Luo et al. also disclose the targeting constructs for BMP-7 gene (see Figure 1). Luo et al. further disclose cells isolated from said mouse (see Figure 2). Therefore, Luo et al. disclose the instantly claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
March 21, 2003

Anne-Marie Falk
ANNE-MARIE FALK, PH.D.
PRIMARY EXAMINER